



## **Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

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# Antiretroviral Management of Newborns with Perinatal HIV Exposure or Perinatal HIV (Last updated November 15, 2017; last reviewed November 15, 2017)

## Panel's Recommendations

- All newborns perinatally exposed to HIV should receive postpartum antiretroviral (ARV) drugs to reduce the risk of perinatal transmission of HIV **(AI)**.
- Newborn ARV regimens—at gestational-age-appropriate doses—should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery **(AII)**.
- The selection of a newborn ARV regimen should be determined based on maternal and infant factors that influence risk of HIV transmission **(AIII)**. The uses of ARV regimens in newborns include:
  - **ARV Prophylaxis:** The administration of one or more ARV drugs to a newborn without confirmed HIV infection to reduce the risk of HIV acquisition
  - **Empiric HIV Therapy:** The administration of a three-drug combination ARV regimen to newborns at highest risk of HIV acquisition. Empiric HIV therapy is intended to be preliminary treatment for a newborn who is later confirmed to have HIV but also serves as prophylaxis against HIV acquisition for those newborns who are exposed to HIV *in utero*, during the birthing process or during breastfeeding and who do not acquire HIV
  - **HIV Therapy:** The administration of a three-drug combination ARV regimen at treatment dosages (antiretroviral therapy [ART]) to newborns with confirmed HIV infection (see [Diagnosis of HIV Infection](#)).
- For newborns whose mothers have received ART during pregnancy with sustained viral suppression near delivery and for whom there are no concerns related to maternal adherence, a 4-week zidovudine ARV prophylaxis regimen can be used **(BII)**.
- Newborns at higher risk of HIV acquisition should receive a combination ARV regimen (ARV prophylaxis or empiric HIV therapy based on clinician assessment of risk), including those born to women with HIV who:
  - Have not received antepartum or intrapartum ARV drugs **(AI)**, or
  - Have received only intrapartum ARV drugs **(AI)**, or
  - Have received antepartum ARV drugs but have not achieved viral suppression near delivery **(AII)**, or
  - Have primary or acute HIV infection during pregnancy **(AII)**, or
  - Have primary or acute HIV infection during breastfeeding **(AII)**.
- Newborns of women with unknown HIV status who test positive on expedited testing performed during labor or shortly after birth should initiate an ARV regimen (ARV prophylaxis or empiric HIV therapy based on clinician assessment of risk) **(AII)**. If supplemental testing is negative, the ARV regimen can be discontinued **(AII)**.
- For newborns with confirmed HIV, ART should be initiated **(AI)**.
- In the United States, the use of ARV drugs other than zidovudine, lamivudine, and nevirapine cannot be recommended for any indication in premature newborns (<37 weeks gestational age) because of lack of dosing and safety data **(BIII)**.
- Providers with questions about ARV management of perinatal HIV exposure should consult the National Perinatal HIV Hotline (1-888-448-8765), which provides free clinical consultation on all aspects of perinatal HIV, including newborn care **(AIII)**.

**Rating of Recommendations:** A = Strong; B = Moderate; C = Optional

**Rating of Evidence:** I = One or more randomized trials in children<sup>†</sup> with clinical outcomes and/or validated endpoints; I\* = One or more randomized trials in adults with clinical outcomes and/or validated laboratory endpoints with accompanying data in children<sup>†</sup> from one or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children<sup>†</sup> with long-term outcomes; II\* = One or more well-designed, nonrandomized trials or observational studies in adults with long-term clinical outcomes with accompanying data in children<sup>†</sup> from one or more similar nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion

<sup>†</sup> Studies that include children or children/adolescents, but not studies limited to post-pubertal adolescents

## General Considerations for Antiretroviral Management of Newborns Exposed to HIV or Born with HIV

All newborns exposed to HIV should receive antiretroviral (ARV) drugs in the neonatal period to reduce perinatal transmission of HIV, with selection of the appropriate type of ARV regimen guided by the

**level of transmission risk.** The most important contributors to the risk of HIV transmission to a newborn exposed to HIV are whether the mother has received antepartum/intrapartum antiretroviral therapy (ART) and her viral load. The risk of transmission is increased in the absence of maternal ART or if maternal antepartum/intrapartum treatment was started after early pregnancy or was ineffective in producing virologic suppression; higher maternal viral load, especially in later pregnancy, correlates with higher risk of transmission. There is a spectrum of transmission risk that depends on these and other maternal and infant factors, including mode of delivery, gestational age at delivery, and maternal health status. **Also, HIV transmission can occur *in utero*, intrapartum, or during breastfeeding.**

Historically, the use of ARV drugs in the newborn period was referred to as ARV prophylaxis since it primarily focused on protection against newborn HIV acquisition. More recently, clinicians have begun to identify newborns at highest risk for HIV acquisition and initiate combination ARV regimens as empiric treatment of HIV. In this guideline, the following terms will be used:

- **ARV Prophylaxis:** The administration of ARV drugs to a newborn without confirmed HIV infection to reduce the risk of HIV acquisition. ARV prophylaxis includes administration of a single agent, usually zidovudine, as well as combinations of two or three ARV drugs.
- **Empiric HIV Therapy:** The administration of a three-drug combination ARV regimen to newborns at highest risk of HIV acquisition. Empiric HIV therapy is intended to be early treatment for a newborn who is later confirmed to have acquired HIV, but also serves as ARV prophylaxis against HIV acquisition for those newborns who are exposed to HIV in utero, during the birthing process, or during breastfeeding and who do not acquire HIV.
- **HIV Therapy:** The administration of a three-drug combination ARV regimen to newborns with confirmed HIV (see [Diagnosis of HIV Infection](#)). HIV therapy is lifelong.

It is noteworthy that, with the important exception of nevirapine, the neonatal ARV dosing for prophylaxis is the same as that for treatment for all ARV drugs currently recommended for newborns. **The terms ARV prophylaxis and empiric HIV therapy describe the clinician's intent in prescribing ARV drugs. At this time, the only difference between ARV prophylaxis containing three ARV drugs and empiric HIV therapy would be the dosage of nevirapine. As newer agents are available for use in newborns, additional differences will emerge.** The interval during which newborn ARV prophylaxis **or empiric HIV therapy** can be initiated and still be of benefit is undefined; however, most studies support providing prophylaxis as early as possible after delivery.<sup>1-6</sup>

**Table 11** provides an overview of neonatal ARV management according to risk of perinatal HIV in the newborn. Data supporting these recommendations are presented later in this section. **Table 12** summarizes the dosing recommendations for ARV dosing in newborns. Additional information about dose selection for newborns, including premature infants (<37 weeks gestational age), can be found in [Pediatric Antiretroviral Drug Information](#). In addition, the [National Perinatal HIV Hotline](#) (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for pregnant women living with HIV and their newborns, and can provide referral to local or regional pediatric HIV specialists.

**Table 11. Newborn Antiretroviral Management According to Risk of HIV Infection in the Newborn**

Drug selection and dosing considerations are related to the age and gestational age of the newborn. Consultation is available through the National Perinatal HIV Hotline (888-448-8765).

Category	Description	Neonatal ARV Management
<b>Low Risk of Perinatal HIV Transmission</b>	Mothers received standard ART during pregnancy with sustained viral suppression near delivery and no concerns related to adherence	4 weeks of ZDV
<b>Higher Risk of Perinatal HIV Transmission<sup>a,b</sup></b>	<ul style="list-style-type: none"> <li>Mothers who received neither antepartum nor intrapartum ARV drugs</li> <li>Mothers who received only intrapartum ARV drugs</li> <li>Mothers who received antepartum and intrapartum ARV drugs but who have detectable viral load near delivery, particularly if delivery was vaginal</li> <li>Mothers with acute or primary HIV infection during pregnancy or breastfeeding<sup>c</sup></li> </ul>	Combination ARV prophylaxis with 6 weeks ZDV and 3 doses of NVP (prophylaxis dosage, with doses given within 48 hours of birth, 48 hours after first dose, and 96 hours after second dose)  or  Empiric HIV therapy consisting of ZDV, 3TC, and NVP (treatment dosage) <sup>d</sup>
<b>Presumed Newborn HIV Exposure</b>	Mothers with unknown HIV status who test positive at delivery or postpartum or whose newborns have a positive HIV antibody test	ARV management as above (for higher risk of perinatal HIV transmission).  ARV management should be discontinued immediately if supplemental testing confirms that mother does not have HIV.
<b>Newborn with Confirmed HIV<sup>e</sup></b>	Confirmed positive newborn HIV virologic test/NAT	3 drug combination ARV regimen at treatment dosage

<sup>a</sup> See text for evidence supporting combination ARV prophylaxis and empiric HIV therapy.

<sup>b</sup> See the [Intrapartum Care](#) section for guidance on indications for scheduled cesarean delivery and intrapartum IV ZDV to reduce the risk of perinatal HIV transmission for mothers with elevated viral load at delivery.

<sup>c</sup> Most experts would opt to administer empiric HIV therapy to infants with acute HIV during pregnancy because of the high risk for *in utero* infection. If acute HIV is diagnosed during breastfeeding, mother should stop breastfeeding.

<sup>d</sup> The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Many experts administer 6 weeks of combination therapy; others opt to discontinue NVP and/or 3TC after the return of negative newborn testing. ZDV should be continued for 6 weeks.

<sup>e</sup> Most experts do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV NAT, given low likelihood of false-positive HIV NAT testing.

**Note:** ARV drugs should be initiated as close to the time of birth as possible, preferably within 6 to 12 hours of delivery. See Table 8 for dosing specifics.

**Key to Acronyms:** 3TC = lamivudine; ART = antiretroviral therapy; ARV =antiretroviral; IV = intravenous; NAT = nucleic acid test; NVP = nevirapine; ZDV = zidovudine

**Table 12. Newborn Antiretroviral Dosing Recommendations**

Drug	Dosing								
<b>ZDV</b> Treatment and Prophylaxis Dosage  <b>Note:</b> For newborns unable to tolerate oral agents, the IV dose is 75% of the oral dose while maintaining the same dosing interval.	<p><u>≥35 Weeks' Gestation at Birth</u>  <i>Birth to Age 4–6 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 4 mg/kg/dose orally twice daily</li> </ul> <p><b>Simplified Weight-Band Dosing for Newborns ≥35 Weeks:</b></p> <table> <tr> <th>Weight Band (kg)</th><th>* Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily</th></tr> <tr> <td>2 to &lt;3 kg</td><td>1 mL</td></tr> <tr> <td>3 to &lt;4 kg</td><td>1.5 mL</td></tr> <tr> <td>4 to &lt;5 kg</td><td>2 mL</td></tr> </table> <p><u>≥30 to &lt;35 Weeks' Gestation at Birth</u>  <i>Birth–Age 2 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 2 mg/kg/dose orally twice daily</li> </ul> <p><i>Age 2 Weeks to 4–6 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 3 mg/kg/dose orally twice daily</li> </ul> <p><u>&lt;30 weeks' Gestation at Birth</u>  <i>Birth–Age 4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 2 mg/kg/dose orally twice daily</li> </ul> <p><i>Age 4–6 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 3 mg/kg/dose orally twice daily</li> </ul>	Weight Band (kg)	* Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily	2 to <3 kg	1 mL	3 to <4 kg	1.5 mL	4 to <5 kg	2 mL
Weight Band (kg)	* Volume (mL) ZDV 10 mg/mL Oral Syrup Twice Daily								
2 to <3 kg	1 mL								
3 to <4 kg	1.5 mL								
4 to <5 kg	2 mL								
<b>3TC</b> <b>Treatment and Prophylaxis Dosage</b>	<p><u>≥32 Weeks' Gestation at Birth:</u>  <i>Birth–Age 4 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 2 mg/kg/dose orally twice daily</li> </ul> <p><i>Age 4–6 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 4 mg/kg/dose orally twice daily</li> </ul>								
<b>NVP</b> Prophylaxis Dosage	<p><u>Birth Weight 1.5–2 kg:</u></p> <ul style="list-style-type: none"> <li>• 8-mg dose orally once daily</li> <li>• <b>Note:</b> No calculation is required for this dose; <b>this is the actual dose, not a mg/kg dose.</b></li> </ul> <p><u>Birth Weight &gt;2 kg:</u></p> <ul style="list-style-type: none"> <li>• 12-mg dose orally once daily</li> <li>• <b>Note:</b> No calculation is required for this dose; <b>this is the actual dose, not a mg/kg dose.</b></li> </ul>								
<b>NVP</b> <b>Treatment Dosage</b>	<p><u>≥37 Weeks' Gestation at Birth</u>  <i>Birth–Age 6 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 6 mg/kg/dose orally twice daily</li> </ul> <p><u>34 to &lt;37 Weeks' Gestation at Birth</u>  <i>Birth–Age 1 Week:</i></p> <ul style="list-style-type: none"> <li>• 4 mg/kg/dose orally twice daily</li> </ul> <p><i>Age 1–6 Weeks:</i></p> <ul style="list-style-type: none"> <li>• 6 mg/kg/dose orally twice daily</li> </ul>								

**Key to Acronyms:** 3TC=lamivudine; IV= intravenous; NVP = nevirapine; ZDV = zidovudine

## ***Recommendations for Antiretrovirals in Specific Clinical Situations***

In the following sections and Table 11, we present available data and recommendations for management of **newborns with confirmed HIV** and newborns born to mothers who:

- Received antepartum/intrapartum ARV drugs with effective viral suppression
- Are at higher risk of transmitting HIV to their newborn, including those who:
  - Received neither antepartum nor intrapartum ARV drugs
  - Received only intrapartum ARV drugs
  - Received antepartum and intrapartum ARV drugs but who have detectable viral load near delivery, particularly if delivery was vaginal
- Have acute or primary HIV infection during pregnancy or breastfeeding
- Have unknown HIV status
- Have known ARV drug-resistant virus

### **Newborns Born to Mothers Who Received Antepartum/Intrapartum Antiretroviral Drugs with Effective Viral Suppression**

The risk of HIV acquisition in newborns born to women who received standard ARV treatment regimens during pregnancy and labor and had undetectable viral loads at delivery is <1%. Zidovudine alone was shown in the PACTG 076 study to effectively reduce perinatal HIV transmission and is recommended as prophylaxis for **neonates whose mothers received ART that resulted in consistent virologic suppression during pregnancy**. The optimal minimum duration of neonatal zidovudine prophylaxis has not been established in clinical trials. A 6-week newborn zidovudine regimen was studied in PACTG 076. However, in the United Kingdom and many other European countries, where a 4-week neonatal zidovudine prophylaxis regimen has been recommended for newborns born to mothers who have received ART regimens during pregnancy and have viral suppression, there has been no apparent increase in the overall HIV perinatal transmission rate.<sup>7,8</sup> In addition, a 4-week zidovudine regimen has been reported to allow earlier recovery from anemia in otherwise healthy newborns compared with the 6-week zidovudine regimen.<sup>9</sup>

Therefore, the Panel on Treatment of Pregnant Women with HIV Infection and Prevention of Perinatal Transmission (the Panel) recommends a 4-week neonatal zidovudine prophylaxis regimen for newborns if the mother has received standard ART during pregnancy with sustained viral suppression (usually defined as confirmed HIV RNA level below the lower limits of detection of an ultrasensitive assay) near delivery and there are no concerns related to maternal adherence. Dosing recommendations for zidovudine are available for premature newborns and an intravenous preparation is available. [Table 12](#) shows recommended neonatal zidovudine dosing based on gestational age and birthweight.

### **Newborns Born to Mothers Who Have Received No Antepartum or Intrapartum Antiretroviral Drugs, Intrapartum Antiretroviral Drugs Only, Who Have Received Combination Antiretroviral Drugs and Do Not Have Viral Suppression Near Delivery, **or Who Have Acquired HIV During Pregnancy or Breastfeeding****

All newborns born to mothers with detectable viral load at the time of delivery, who received only intrapartum ARV drugs, or who have received no ARV drugs during pregnancy or delivery, are at higher risk of HIV acquisition and should receive combination ARV prophylaxis **or empiric HIV therapy**.<sup>5,10-14</sup> **The experience with combination ARV prophylaxis and empiric HIV therapy is described below. At this time, the optimal duration of combination ARV regimens or empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Many experts administer 6 weeks of combination therapy; others opt to discontinue nevirapine and/or lamivudine after the return of negative newborn testing but continue zidovudine for 6 weeks.**

For those women who received ARV drugs during pregnancy, but have a detectable viral load near delivery, the level of viremia in the mother that would trigger the use of combination newborn prophylaxis is not definitively known. In 2 large observational studies of women on combination antenatal ARV drugs, perinatal transmission rates were 0.05% and 0.3% when the mother had viral load measurements <50 copies/mL at delivery. Rates of transmission increased to 1.1% and 1.5% when viral load measurements were 50 to 399 copies/mL and 2.8% and 4.1% when viral load measurements were >400 copies/mL.<sup>15,16</sup> However, there has been no study to demonstrate relative efficacy of combination **ARV regimens, including prophylaxis regimens and empiric HIV therapy**, compared to standard newborn prophylaxis at these different thresholds of maternal viremia. While some experts would recommend a combination ARV regimen or empiric HIV therapy with any level of detectable viremia, others reserve combination regimens and empiric HIV therapy until higher levels of maternal viral load are documented. The decision to administer a combination prophylaxis regimen or empiric therapy should be made following discussion with the parents weighing the risks and benefits of **the proposed regimen**.

**Primary or acute HIV infection during pregnancy is associated with an increased risk of perinatal transmission of HIV. Combination ARV prophylaxis or empiric HIV therapy should be administered to the infant until HIV can be confirmed or ruled out. (see [Acute HIV Infection](#)).**

**In summary, in these scenarios where the infant is at higher risk of HIV transmission, the Panel recommends either combination ARV prophylaxis or empiric HIV therapy. The data supporting the use of combination ARV prophylaxis regimens and empiric HIV therapy are summarized below. Choosing between combination ARV prophylaxis and empiric HIV treatment will depend on the clinician assessment of the likelihood of HIV transmission.**

### **Combination Antiretroviral Prophylaxis**

There is a paucity of data from randomized clinical trials to guide the optimal selection of a newborn combination prophylaxis regimen. To date, the NICHD-HPTN 040/PACTG 1043 trial is the only randomized clinical trial of combination prophylaxis in newborns at high risk of HIV acquisition. In this study, 1,746 formula-fed newborns born to women with HIV who did not receive any ARV drugs during pregnancy were randomized to 1 of 3 newborn prophylaxis regimens: the standard 6-week zidovudine regimen; 6 weeks of zidovudine plus three doses of nevirapine given during the first week of life (first dose at birth–48 hours, second dose 48 hours after first dose, and third dose 96 hours after second dose); and 6 weeks of zidovudine plus 2 weeks of lamivudine/nelfinavir. Forty-one percent of mothers received zidovudine during labor. The risk of intrapartum transmission was significantly lower in the 2- and 3-drug arms (2.2% and 2.5%, respectively, vs. 4.9% for 6 weeks of zidovudine alone;  $P = .046$  for each experimental arm vs. zidovudine alone).<sup>5</sup> **The NICHD-HPTN 040/PACTG 1043 regimen was associated with nucleoside reverse transcriptase inhibitor (NRTI) resistance in 3/53 (5.7%) participants with *in utero* infection who were treated with zidovudine alone and in 6/33 (18.2%) participants treated with zidovudine plus nevirapine ( $P > 0.05$ ). In addition, the third drug in the three-arm regimen was nelfinavir, which has highly variable kinetics in this age group and did not reach the kinetic target in 46% of study participants.<sup>17</sup>** Although transmission rates with the two combination regimens were similar, neutropenia was significantly more common with the three-drug regimen than with the two-drug or zidovudine-alone regimen (27.5% vs. 15%,  $P < 0.0001$ ).

Data from Europe and the United States indicate increasing use of combination ARV prophylaxis in newborns exposed to HIV. In the United Kingdom and Ireland, use increased from 9% of newborns exposed to HIV in 2001 to 2004 to 13% between 2005 to 2008 and, in a poll of 134 U.S.-based providers, 62% reported using combination prophylaxis in high-risk newborns.<sup>18-20</sup> However, interpretation of these observational studies is complicated by the definition of combination ARV prophylaxis, **use of prophylaxis versus treatment dosing of nevirapine**, and combining heterogeneous combination ARV prophylaxis regimens to compare safety and efficacy with zidovudine monotherapy. Many studies include single-dose nevirapine in combination with another ARV, usually zidovudine, as combination therapy. Most do not report whether nevirapine was administered at the **recommended** prophylaxis dose or at a higher dose **as part of empiric HIV therapy**. So,

despite increasing utilization of various combination ARV prophylaxis regimens, comprehensive data on efficacy and safety are lacking. Therefore, based on the NICHD-HPTN 040/PACTG 1043 trial, the 2-drug regimen of 6 weeks of zidovudine plus 3 doses of nevirapine is the combination ARV prophylaxis regimen recommended by the Panel for newborns at higher risk of HIV acquisition ([Tables 11](#) and [12](#)).

### **Empiric HIV Therapy**

A three-drug ARV regimen including zidovudine, lamivudine, and the treatment dose of nevirapine (**empiric HIV therapy**) is the other option recommended by the Panel for newborns at high risk of HIV acquisition.

Enthusiasm for this approach followed a case of a “functional cure” of HIV in an newborn reported in 2013.<sup>21</sup> The newborn was born by vaginal delivery at 35 weeks’ gestation to a woman who received no prenatal care and was diagnosed as having HIV by expedited testing during labor; delivery occurred before maternal intrapartum ARV drugs could be given. At age 30 hours, the newborn initiated a regimen of zidovudine, lamivudine, and nevirapine (the latter drug administered at a higher treatment dose rather than standard prophylactic dosing). The newborn was found to have a positive HIV DNA polymerase chain reaction (PCR) in a sample obtained at age 30 hours and an HIV RNA level of 19,812 copies/mL on an HIV RNA PCR assay performed at age 31 hours. Based on these tests, the newborn was continued on treatment for HIV, thought to be acquired *in utero*. At age 18 months, the mother discontinued ART; levels of plasma RNA, proviral DNA, and HIV antibodies remained undetectable in the child for over 2 years without ART. Unfortunately, virologic rebound was identified shortly before the child turned 4 years of age. Of interest, another case of virologic rebound following 4 years of suppression in a newborn treated since birth has subsequently been reported.<sup>22</sup>

Further support of empiric HIV therapy comes from Canadian investigators who have reported outcomes in 136 newborns considered at high risk of HIV acquisition (i.e., born to women with HIV who had detectable viral load and/or poor adherence to therapy prior to delivery) who received a triple-ARV regimen within 72 hours of birth. Of these 136 newborns, 12 (9%) were found to have acquired HIV and no major toxicities were identified.<sup>23</sup> However, there was no control group to permit comparison of safety or efficacy of this approach relative to single-drug or two-drug regimens. Another Canadian study compared the safety of empiric HIV therapy in 148 newborns with high-risk exposure (i.e., incomplete maternal virologic suppression at delivery or, in the absence of maternal viral load results, a maternal history of incomplete adherence or non-adherence to ART, or late pregnancy initiation of ART) and 145 control low-risk newborns who received only zidovudine. Thirteen newborns in the empiric HIV therapy group acquired HIV, including 5 with a positive HIV nucleic acid test (NAT) within the first 48 hours of life, suggesting *in utero* infection. No newborn in the low-risk zidovudine-only group acquired HIV. The newborns receiving empiric HIV therapy demonstrated more non-specific signs and symptoms (e.g., vomiting, diarrhea, rash, jitteriness, irritability) potentially attributable to medication-related adverse effects compared to none of the newborns receiving zidovudine only (10.2% vs. 0%,  $P < 0.001$ ). ARV drugs were also more likely to be discontinued prematurely in the newborns receiving empiric HIV therapy (9.5% vs. 2.1%,  $P = 0.01$ ).<sup>24</sup>

Empiric HIV therapy in newborns is consistent with the Centers for Disease Control and Prevention recommendations for occupational and non-occupational post-exposure prophylaxis in adults, where risk of infection is often lower than in newborns at high risk of HIV acquisition.<sup>25,26</sup> However, there are two key safety issues related to the choice and dose of ARV drugs in these newborns. First, although the use of nevirapine to prevent perinatal transmission has been found to be safe in neonates and low-birthweight newborns, these prophylaxis-dose regimens target trough drug levels at least 10-fold lower than targeted therapeutic levels. The optimal dose for empiric HIV therapy in newborns has not been sufficiently studied but studies are ongoing. Second, lopinavir/ritonavir is not recommended for neonates younger than age 14 days because of the potential for significant toxicity (see [Short-Term Antiretroviral Drug Safety and Choice for Neonatal Prophylaxis](#)). Therefore, the risks of empiric HIV therapy in terms of newborn toxicity (particularly in preterm newborns) and efficacy require further study before a general recommendation can be made.

There are three ongoing clinical trials investigating newborn empiric HIV therapy containing nevirapine at

treatment doses, zidovudine, and lamivudine shortly after birth in newborns at high risk of HIV infection (international multisite IMPAACT P1115, ClinicalTrials.gov identifier NCT02140255), or those known to have HIV (BHP-074 in Botswana, NCT02369406, and the Leopard Study in South Africa, NCT02431975). Additional safety and pharmacokinetic (PK) data from these studies will guide future recommendations.

At this time, if an empiric HIV therapy regimen is selected, the Panel recommends a combination of zidovudine, lamivudine, and nevirapine (treatment dosage) (see [Tables 11 and 12](#)). The optimal duration of empiric HIV therapy in newborns at higher risk of perinatal HIV transmission is unknown. Many experts administer 6 weeks of combination therapy; others opt to discontinue nevirapine and/or lamivudine after the return of a negative newborn testing. Zidovudine should be continued for 6 weeks.

### **Newborns Born to Mothers with Unknown HIV Status at Presentation in Labor**

Expedited HIV testing of mothers is recommended during labor for women with unknown HIV status and for mothers and/or newborns as soon as possible after birth if expedited HIV testing was not performed during labor (see [Identification of Perinatal Exposure](#)). Expedited test results should be available within 60 minutes. If expedited testing is positive, newborn combination ARV prophylaxis or empiric HIV therapy should be initiated immediately, without waiting for the results of supplemental tests as described below. Expedited HIV testing should be available on a 24-hour basis at all facilities with a maternity service and/or neonatal intensive care, special care or newborn nursery.

A positive initial test result in mothers or newborns should be presumed to indicate maternal HIV until standard supplemental testing clarifies maternal and newborn status. If appropriate test results on a mother (or newborn) are negative, newborn ARV drugs can be discontinued. Clinicians should be aware of their state laws, as there is variability in the testing allowed without parental consent.

Breastfeeding should be stopped until HIV is confirmed or ruled out in a woman who is suspected of having HIV based on an initial positive antibody or antibody/antigen test result. Pumping and temporarily discarding or freezing breast milk can be recommended. If HIV is ruled out, breastfeeding can resume. If HIV is confirmed, breastfeeding should be discontinued permanently.<sup>27</sup>

### **Newborns Born to Mothers with Antiretroviral Drug-Resistant Virus**

The optimal ARV regimen for newborns delivered by women with ARV drug-resistant virus is unknown. It is also unknown whether resistant virus in the mother increases the risk of HIV acquisition by the infant. The ARV regimen for newborns born to mothers with known or suspected drug resistance should be determined in consultation with a pediatric HIV specialist before delivery or through consultation with the [National Perinatal HIV Hotline](#) (888-448-8765). However, there is no evidence that neonatal prophylaxis regimens customized based on presence of maternal drug resistance are more effective than standard neonatal prophylaxis regimens.

Data from the WITS study suggest that, in women who have mixed zidovudine-resistant and zidovudine-sensitive viral populations, the zidovudine-sensitive virus may be preferentially transmitted.<sup>28,29</sup> Thus, the selection of the newborn ARV regimen should be based on other risk factors ([Table 11](#)).

Some studies have suggested that ARV drug-resistant virus may have decreased replicative capacity (reduced viral fitness) and transmissibility.<sup>29</sup> However, perinatal transmission of multidrug-resistant virus has been reported both in the United States and in international settings.<sup>30-34</sup>

### **Newborns with Confirmed HIV**

Until recently, neonatal ARV regimens were designed for prophylaxis against perinatal HIV transmission and to be as simple as possible for practical use. There was little reason to develop ARV regimens for treatment of neonates, as the long turnaround times to receive HIV NAT testing results meant that neonatal infections were generally not diagnosed in the first weeks of life. HIV NAT test results now often are available within a few days and newborns with HIV are being diagnosed as early as the first days of life. A positive HIV NAT

test must be repeated to confirm HIV. However, most experts do not recommend delaying the initiation of ART while waiting for the results of the confirmatory HIV NAT, given low likelihood of false-positive HIV NAT testing. However, evidence that very early treatment (before age 2 weeks) will produce a prolonged remission or lead to better outcomes in newborns with HIV is lacking. Earlier diagnosis of HIV in newborns and the increasing use of empiric HIV therapy in newborns at high risk for HIV acquisition have necessitated investigation of dosing and safety of ARV drugs in term and preterm newborns. Although still incomplete, especially for preterm newborns, PK and safety profiles of ARV drugs are increasingly available. As already noted, the recommended neonatal ARV doses for prophylaxis and for treatment are the same with the important exception of nevirapine (see [Pediatric Antiretroviral Drug Information](#)).

Sufficient data exist to provide dosing recommendations appropriate for the treatment of HIV in neonates using the following medications (see Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection):

- From birth in term and preterm newborns: [zidovudine](#), [lamivudine](#), [nevirapine](#)
- From birth in term neonates: [emtricitabine](#), [raltegravir](#)
- From age 2 weeks in term neonates: [lopinavir/ritonavir](#)

Dosing recommendations for *premature* newborns are available for only zidovudine, [lamivudine](#), and nevirapine. Neonatal dosing advice, including for premature newborns, is summarized in Table 8. For more detailed information about neonatal dosing recommendations and considerations of these drugs, please see the [Pediatric Antiretroviral Drug Information](#) for these drugs.

### **Newborns of Mothers Diagnosed with HIV while Breastfeeding**

Women with suspected HIV (e.g., a positive initial screening test) should stop breastfeeding until HIV is ruled out. Pumping and temporarily discarding or freezing breast milk can be recommended to mothers who are suspected of having HIV but whose HIV serostatus is not yet confirmed and who want to continue to breastfeed. If HIV is ruled out, breastfeeding can resume. Breastfeeding is not recommended for women with confirmed HIV in the United States, including those receiving ART (see [Newborn Feeding Practices and Risk of HIV Transmission](#)).<sup>35</sup>

The risk of HIV acquisition associated with breastfeeding depends on multiple newborn and maternal factors, including maternal viral load and CD4 T lymphocyte (CD4) cell count.<sup>36</sup> Newborns of women who develop acute HIV while breastfeeding are at greater risk of acquiring HIV than are those whose mothers have chronic HIV infection<sup>37</sup> because acute HIV infection is accompanied by a rapid increase in viral load and a corresponding decrease in CD4 cell count.<sup>38</sup>

Other than discontinuing breastfeeding, optimal strategies for managing a newborn who was breastfed by a mother with HIV (often because the mother just learned of her own HIV diagnosis) have yet to be defined. Some experts would consider the use of post-exposure prophylaxis in newborns for 4 to 6 weeks after cessation of breastfeeding. Post-exposure prophylaxis, however, is less likely to be effective in this circumstance compared with other non-occupational exposures because the exposure to breast milk is likely to have occurred over a prolonged period rather than in a single exposure.<sup>39</sup>

Several studies of newborns breastfed by women with chronic HIV infection in low-resource settings have shown that daily newborn nevirapine, lamivudine, lopinavir/ritonavir or nevirapine plus zidovudine can reduce the risk of postnatal infection during breastfeeding.<sup>40-44</sup> No trials have evaluated the use of combination regimens for preventing transmission after cessation of breastfeeding in mothers with acute HIV infection.

Because of the high risk of postnatal transmission from a breastfeeding woman with acute HIV infection, an alternative approach favored by some experts would be to offer empiric HIV therapy until infant status can be determined. If the infant's initial HIV NAT is negative, the optimal duration of empiric HIV therapy is unknown. A 28-day course may be reasonable based on current recommendations for non-occupational

HIV exposure.<sup>39</sup> As in other situations, decisions regarding ARV management should be accompanied by consultation with a pediatric HIV specialist and maternal counseling on the potential risks and benefits of this approach. The [National Perinatal HIV Hotline](https://www.hiv.gov/national-perinatal-hiv-hotline) (888-448-8765) is a federally funded service providing free clinical consultation for difficult cases to providers caring for pregnant women living with HIV and their newborns, and can provide referral to local or regional pediatric HIV specialists.

Newborns should be tested for HIV **prior to initiation of** empiric HIV therapy and 4 to 6 weeks, 3 months, and 6 months after recognition of maternal HIV and cessation of breastfeeding to determine HIV status. (see [Diagnosis](#) section). If a newborn is already receiving an ARV prophylaxis regimen other than empiric HIV therapy and is found to have HIV, prophylaxis should be discontinued and treatment for HIV initiated. Resistance testing should be performed, and the ART regimen modified if needed (see the [Pediatric Antiretroviral Guidelines](#)).

### ***Short-Term Antiretroviral Drug Safety***

Newborn prophylaxis with zidovudine has been associated with only minimal toxicity, consisting primarily of transient hematologic toxicity (mainly anemia), which generally resolves by age 12 weeks (see [Initial Postnatal Management](#)). Data are limited on the toxicity to newborns of exposure to multiple ARV drugs.

Other than zidovudine, lamivudine is the NRTI with the most experience in use for neonatal prophylaxis. In early studies, neonatal exposure to combination zidovudine/lamivudine was generally limited to 1/3, 4/5, 4/6 or 2 weeks.<sup>5</sup> Six weeks of newborn zidovudine/lamivudine exposure also has been reported; these studies suggest that hematologic toxicity may be increased over that seen with zidovudine alone, although the newborns also had in utero exposure to maternal combination therapy.

In a French study, more severe anemia and neutropenia were observed in newborns exposed to 6 weeks of zidovudine/lamivudine for prophylaxis plus maternal antepartum zidovudine/lamivudine than in a historical cohort exposed only to maternal and newborn zidovudine. Anemia was reported in 15% and neutropenia in 18% of newborns exposed to zidovudine/lamivudine, with 2% of newborns requiring blood transfusion and 4% requiring treatment discontinuation for toxicity.<sup>47</sup> Similarly, in a Brazilian study of maternal antepartum and 6-week newborn zidovudine/lamivudine prophylaxis, neonatal hematologic toxicity was common, with anemia seen in 69% and neutropenia in 13% of newborns.<sup>48</sup>

Experience with other NRTI drugs for neonatal prophylaxis is more limited.<sup>49,50</sup> Hematologic and mitochondrial toxicity may be more common with exposure to multiple versus single NRTI drugs.<sup>47,51-54</sup>

In rare cases, chronic multiple-dose nevirapine prophylaxis in pregnant women has been associated with severe and potentially life-threatening rash and hepatic toxicity.<sup>55</sup> These toxicities have not been observed in newborns receiving prophylactic dosing with single-dose nevirapine, the two-drug zidovudine regimen plus three doses of nevirapine in the first week of life in NICHD-HPTN 040/PACTG 1043), or in breastfeeding newborns receiving nevirapine prophylaxis daily for 6 weeks to **18** months to prevent transmission of HIV via breast milk.<sup>5,40-42,44,56</sup>

Of the protease inhibitors, pediatric drug formulations are available for lopinavir/ritonavir, ritonavir, darunavir, tipranavir, and fosamprenavir, but their use in neonates in the first weeks of life is not recommended due to lack of dosing and safety information. In addition, lopinavir/ritonavir oral solution contains 42.4% alcohol and 15.3% propylene glycol, and enzymes that metabolize these compounds are immature in neonates, particularly preterm newborns. Four premature newborns (2 sets of twins) started on lopinavir/ritonavir from birth, developed heart block that resolved after drug discontinuation.<sup>57,58</sup> In studies of adults, both ritonavir and lopinavir/ritonavir cause dose-dependent prolongation of the PR interval, and cases of significant heart block, including complete heart block, have been reported. Elevation of 17-hydroxyprogesterone and dehydroepiandrosterone-sulfate has also been associated with administration of lopinavir/ritonavir compared with zidovudine in the neonatal period. Levels of 17-hydroxyprogesterone were greater in newborns who were also exposed to lopinavir/ritonavir in utero compared with those exposed

only in the neonatal period. Term newborns were asymptomatic but three premature newborns experienced life-threatening symptoms compatible with adrenal insufficiency, including hyponatremia and hyperkalemia with, in one case, cardiogenic shock.<sup>59</sup> Based on these and other post-marketing reports of cardiac toxicity (including complete atrioventricular block, bradycardia, and cardiomyopathy), lactic acidosis, acute renal failure, adrenal dysfunction, central nervous system depression, respiratory complications leading to death, and metabolic toxicity,<sup>60</sup> predominantly in preterm neonates, the U.S. Food and Drug Administration (FDA) now recommends that lopinavir/ritonavir oral solution **not** be administered to neonates before a postmenstrual age (first day of the mother's last menstrual period to birth plus the time elapsed after birth) of 42 weeks and a postnatal age of at least 14 days.<sup>61</sup> However, a recent study (ANRS 12174) randomized 1,273 newborns, 615 assigned to lopinavir/ritonavir and 621 assigned to lamivudine, as prophylaxis during breastfeeding in women with CD4 counts above the local threshold for treatment at the time. Newborn study prophylaxis was initiated at 7 days of life and only newborns greater than 2 kg were randomized. Clinical and biological severe adverse events did not differ between groups suggesting that lopinavir/ritonavir is safe in term newborns, 7 days of age and older.<sup>62</sup> At this time, the Panel does not recommend the use of lopinavir/ritonavir before a postmenstrual age of 42 weeks and a postnatal age of at least 14 days.

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